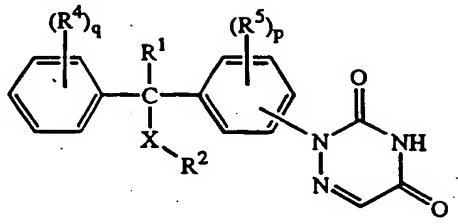
Claims

1. A compound of formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

q represents an integer being 0, 1, 2, 3, 4 or 5;

X represents O, S, NR^3 or a direct bond;

R^1 represents hydrogen, hydroxy, halo, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, aminoC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl or mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkylamino;

R^2 represents aryl, Het^1, C_{3-7}cycloalkyl, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^3, then R^2 may also represent aminocarbonyl, aminothiocarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylthiocarbonyl, arylcarbonyl or arylthiocarbonyl;

R^3 represents hydrogen or C_{1-4}alkyl;

each R^4 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

each R^5 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, arylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or

di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, Het^3 and R^6;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, Het^3 and R^6;

each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C1-4alkyloxy, carboxyl, C1-4alkyloxycarbonyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, $C(=O)NR^7R^8$, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide-2-yl, Het^3 and $C(=O)Het^3$;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl and R^6;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, halo, hydroxy, C1-4alkyl, C1-4alkyloxy, polyhaloC1-4alkyl, NR^9R^{10}, R^6, phenyl, Het^3 and C_{1-4}alkyl substituted with NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl, imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11};

Het^2 represents a monocyclic heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl,

isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl and triazinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with R^{11};

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two or three substituents each independently selected from C_{1-4}alkyl, C_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, phenylC_{1-4}alkyl, piperidinyl, $NR^{12}R^{13}$, R^6 and C_{1-4}alkyl substituted with R^6 or $NR^{12}R^{13}$.

2. A compound according to claim 1 wherein R^1 is hydrogen, hydroxy, halo, amino, C_{1-6}alkyl, C_{1-6}alkyloxy or mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkylamino.

3. A compound according to claim 1 or 2 wherein R^2 is aryl, Het^1, C_{3-7}cycloalkyl, or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^3, then R^2 may also represent aminocarbonyl, aminothiocarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylthiocarbonyl, arylcarbonyl or arylthiocarbonyl.

4. A compound according to any one of claims 1 to 3 wherein the 6-azauracil moiety is in the para position relative to the central carbon atom.

5. A compound according to any one of claims 1 to 4 wherein q is 1 or 2 and one R^4 substituent is in the 4 position; and p is 1 or 2 and the one or two R^5 substituents are in the ortho position relative to the central carbon atom.

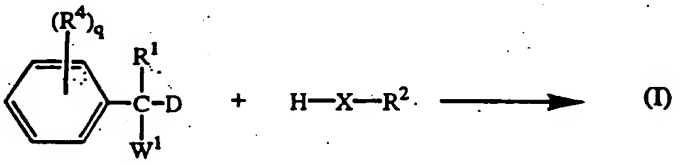
6. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.

7. A process for preparing a composition as claimed in claim 6, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 5.

8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

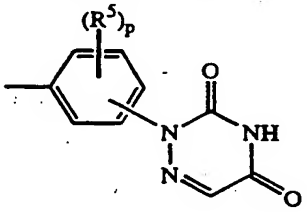
9. Use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.

10. A process for preparing a compound as claimed in claim 1, characterized by,
a) reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and in the presence of a base;



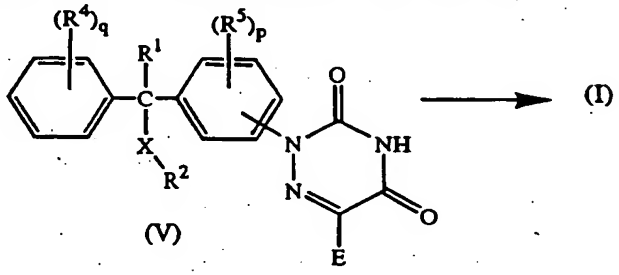
(II) (III) (I)

wherein R^1, R^2, R^4, X and q are as defined in claim 1, and D represents



wherein R^5 and p are defined as in claim 1;

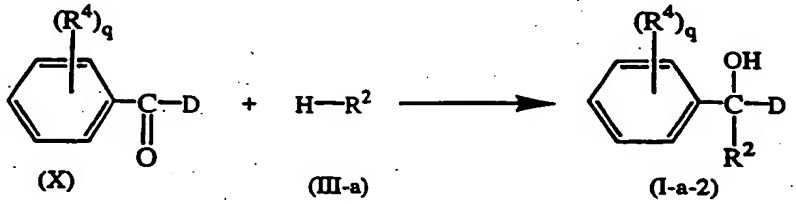
b) eliminating the group E of a triazinedione of formula (V)



(V) (I)

wherein R^1, R^2, R^4, R^5, X and q are as defined in claim 1;

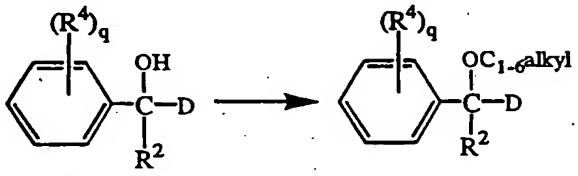
c) reacting a ketone of formula (X) with an intermediate of formula (III-a) in the presence of a base and in a reaction-inert solvent; thus obtaining a compound of formula (I-a-2);



(X) (III-a) (I-a-2)

wherein R^2, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

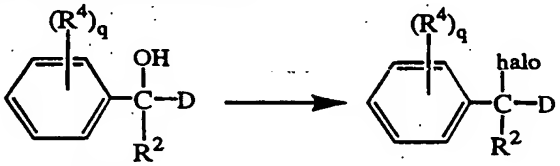
d) converting a compound of formula (I-a-2) to a compound of formula (I-a-3) using art-known group transformation reactions,



(I-a-2) (I-a-3)

wherein R^2, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

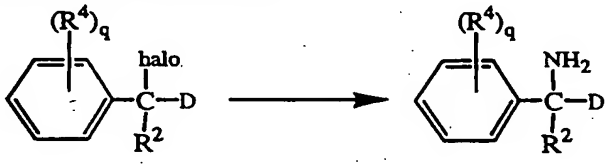
e) converting a compound of formula (I-a-2) to a compound of formula (I-a-4) using art-known group transformation reactions,



(I-a-2) (I-a-4)

wherein R^2, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

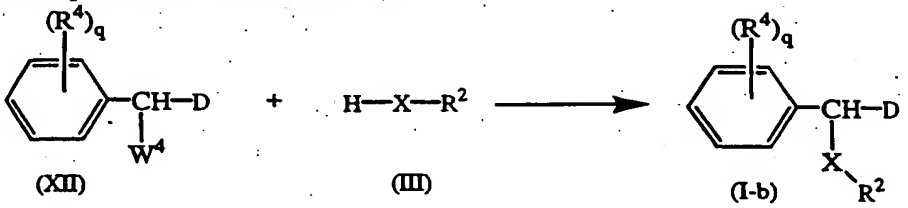
f) converting a compound of formula (I-a-4) to a compound of formula (I-a-5) using art-known group transformation reactions,



(I-a-4) (I-a-5)

wherein R^2, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

g) reacting an intermediate of formula (XII) wherein W^4 is a suitable leaving group with an intermediate of formula (III) optionally in the presence of a suitable base; thus obtaining a compounds of formula (I-b);

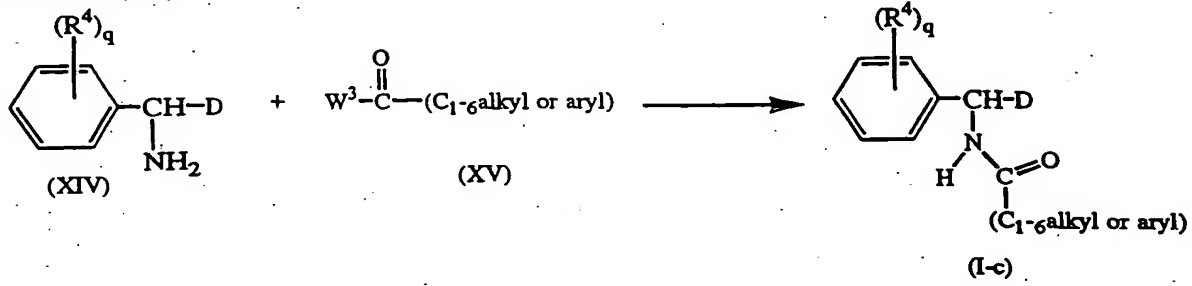


(XII) (III) (I-b)

wherein R^2, R^4, X and q are as defined in claim 1 and D is defined as in claim 9a);

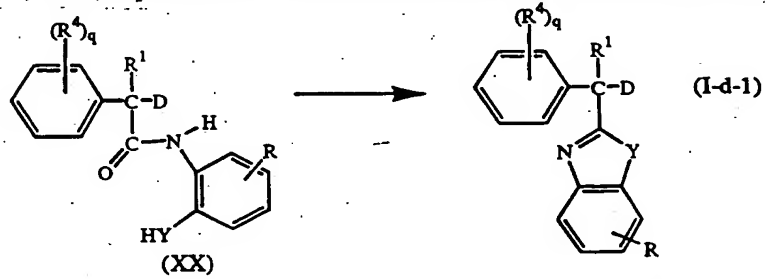
h) reacting an intermediate of formula (XIV) with an intermediate of formula (XV) wherein W^3 is a suitable leaving group, in the presence of a suitable base and

optionally in the presence of a reaction-inert solvent; thus obtaining a compound of formula (I-c);



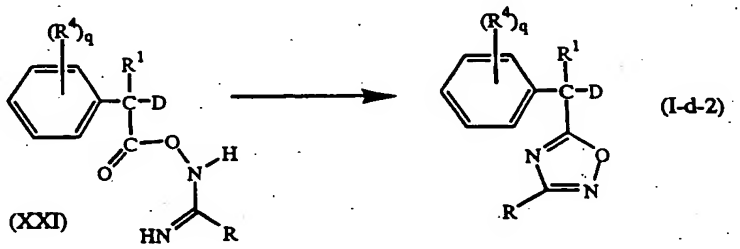
wherein R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

i) cyclizing an intermediate of formula (XX) wherein Y is O, S or NR^3, to a compound of formula (I-d-1), in the presence of a suitable solvent at an elevated temperature;



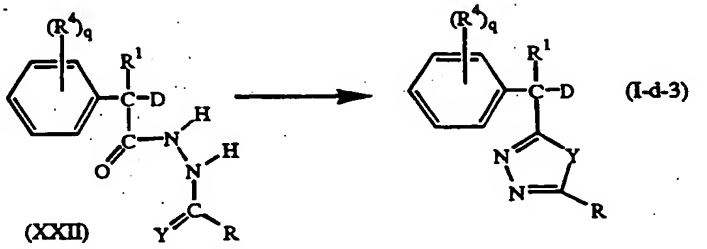
wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

j) cyclizing an intermediate of formula (XXI) to a compound of formula (I-d-2) in a reaction-inert solvent at an elevated temperature,



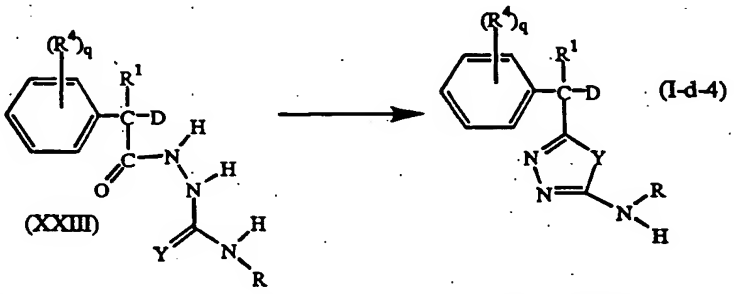
wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

k) cyclizing an intermediate of formula (XXII) wherein Y is O, S or NR^3, to a compound of formula (I-d-3), in a suitable solvent,



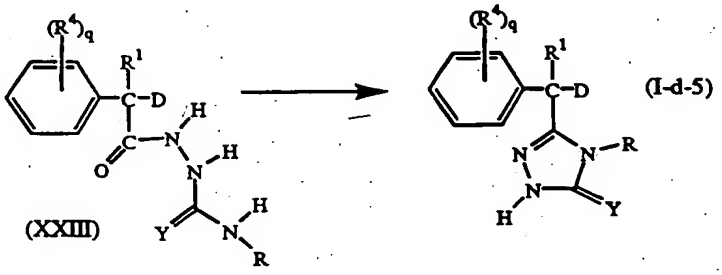
wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

l) cyclizing an intermediate of formula (XXIII) wherein Y is O, S or NR^3, to a compound of formula (I-d-4), in a reaction-inert solvent and in the presence of an acid,



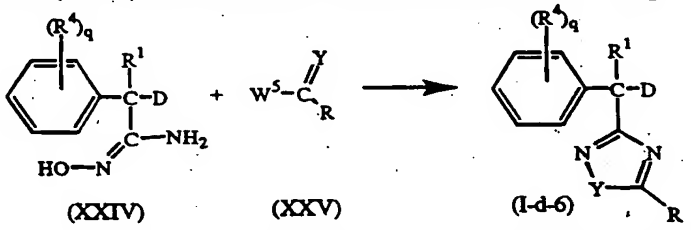
wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

m) cyclizing an intermediate of formula (XXIII) wherein Y is O, S or NR^3, to a compound of formula (I-d-5), in a reaction-inert solvent and in the presence of an acid,



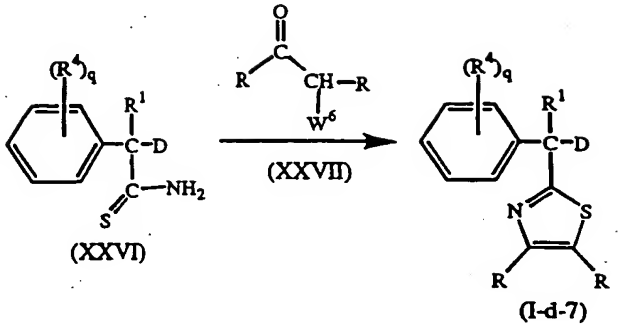
wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

n) reacting an intermediate of formula (XXIV) with an intermediate of formula (XXV) wherein Y is O, S or NR^3, and W^5 is a suitable leaving group; thus forming a compound of formula (I-d-6) in a reaction-inert solvent and in the presnece of a base,



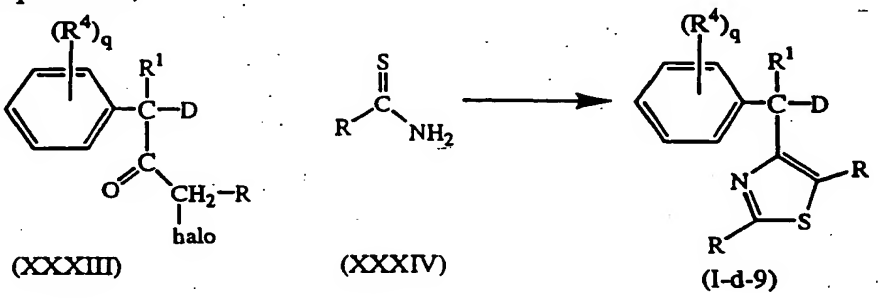
wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

o) reacting an intermediate of formula (XXVI) with an intermediate of formula (XXVII) wherein W^6 is a suitable leaving group; thus forming a compound of formula (I-d-7), in a reaction-inert solvent and in the presnece of an acid;



wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

p) reacting an intermediate of formula (XXXIII) with a thioamide of formula (XXXIV); thus forming a compound of formula (I-d-9) in a reaction-inert solvent at an elevated temperature;



wherein R, R^1, R^4 and q are as defined in claim 1 and D is defined as in claim 9a);

and if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

11. A process of marking a receptor comprising the steps of
    a) radiolabelling a compound as defined in claim 1;
    b) administering said radiolabelled compound to biological material,
    c) detecting the emissions from the radiolabelled compound.

12. A process of imaging an organ, characterized by, administering a sufficient amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.